UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

KM

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/244,130	02/04/99	DUJON	B	3495.0111-10

HM22/0411

FINNEGAN HENDERSON FARABOW
GARRETT AND DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

EXAMINER	
KAUSHAL, S	
ART UNIT	PAPER NUMBER
1633	15

DATE MAILED: 04/11/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/244,130	DUJON ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/06/00 and 01/24/01* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 12/06/00 and 01/24/01 has been fully considered. Claims 23-47 are canceled. Claims 48-93 are pending and are examined in this office action.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/24/01 has been entered.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of

record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 53-57 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15, 28, 29, 30, 32 of co-pending Application No.08/643732. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 15, 28, 29, 30, 32 of 08/643,732 are drawn to a non-human transgenic animal (mouse) comprising a cell encoding an I-SceI site, which encompasses the subject matter of claims 53-57 of instant application. The scope of instant invention embrace a transgenic mice encoding any and all Group I intron encoded endonuclease sites, which encompass a transgenic mice encoding I-SceI site. Thus, the invention of instant claims is an obvious extension of transgenic mouse encoding a Group I intron encoded endonuclease site (I-SceI).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 48-93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a transgenic mouse encoding Group I interon encoded endonuclease and a transgenic mouse encoding Group I intron encoded enonuclease recoginition site. The claims are further drawn to a method of generating and culturing transgenic cells from the transgenic mice as claimed. In addition the claims are further drawn to a method of activation of a specific gene in the mouse cells by cleaving a Group I intron encoded endonuclease recognition site, wherein the recognition site is inserted into a gene.

Applicant is referred to the Interim guidelines on *Written Description* published December 21, 1999 in the Federal Register, Vol. 64, No. 244, pp. 71427-71440 (also available at www.uspto.gov). In analyzing whether the written description requirement is met for the claimed invention, it is first determined whether a claimed genus have been described through sufficient description of a representative number of species by their complete structure and function. Although, it is not realistic to expect that the "complete structure" of an animal, or even a cell, could be described, the phenotype a transgenic animal with desired traits remains unpredictable phenomenon because it is the result of a complex interaction between animal genetics and environment. Therefore, the inquiry required by this portion of the written description guidelines is interpreted to be whether the phenotypic consequences of altering the genotype have been described.

In this case, the few disclosed embodiments are not representative of the products claimed. The claims encompass a transgenic mouse and recombinant cells provided from the transgenic mouse, comprising a nucleotide sequence encoding Group-I intron encoded i) endonucleases and ii) recognition sites. The Group-I intron encoded endonucleases encompass any and all endonucleases encompassed by Class I, II, III, IV, and V I-endonucleases, wherein the Class I I-endonucleases encompass I-SceI, I-SceIV, I-CsmI and PanI endonucleases. The invention as claimed encompass transgenic mice encoding any and all Group-I intron encoded endonucleases. Next, it is then determined whether a representative number of species have been sufficiently described. At best the specification only discloses **a transgenic yeast or transformed/transfected mouse cell lines (NIH3T3, PCC7-s)**. The specification fails to describe a single transgenic mouse encoding the Group-I intron encoded endonucleases

(including I-SceI). The transgenic yeast cells and/or transformed mouse cell lines, neither represents nor predicts the phenotypic characteristic of transgenic mouse as claimed. The limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that applicants were in possession of a transgenic mouse and/or recombinant cells (as claimed) at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed invention.

4. Claims 48-93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to **make and/or use** the invention.

The invention as claimed is described above under section-3.

Applicant's arguments filed 12/04/00 (page 5-8) have been fully considered but they are unpersuasive. The applicant argues that applicants are not required to disclose a working example of the claimed invention. The applicant further argues that test of enablement is not whether any experimentation is necessary but whether, if experimentation is necessary, it is undue (response, page 6, para. 2). The applicant further argues that no undue experimentation is required to produce the claimed invention because D3 embryonic stem cells containing I-Sce I site can be used to generate the claimed transgenic mice (response, page 7, para. 1). In addition, citing Viville the applicant concluded that generation of transgenic mice from D3 embryonic stem cells line would require only routine experimentation.

However this is found unpersuasive because the state of transgenic art at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment. (Wood. Comp. Med. 50(1): 12-15, 2000, see page12). The phenotype examined in a transgenic and knock out model is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. The genes may be part of same biochemical or signaling pathway or of an opposing pathway or may appear

unrelated to the gene being studied. Furthermore, allelic variations and the interactions between the allelic variants also influence a particular phenotype. These epigenetic effects can dramatically alter the observed phenotype and therefore can influence or later the conclusions drawn form the transgenic or knockout models (Sigmund, Arterioscler. Throm. Vasc. Biol.20:1425-1429, 2000, see page 1425). The transgene expression and physiological consequences of transgene products in non-mouse mammals are not always accurately predicted among various species of mammals (Wall RJ Theriogenology 45:57-68, 1996). Transgene efficiency is low, and range from 1% in farm animals (cattle, sheep, pigs) to 3% in laboratory animals like rabbits, mice and rats (Wall, see page 61). Furthermore, the lack of understanding of essential genetic control elements make it difficult to predict the behavior of a transgene in any and all animals because the expression is influenced by position effect in transgenic animals. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, are the important factors that govern the expression of a transgene (Wall, page 61-62). The cis acting elements of one species may interact with different transactivating factors in other species. For example, the introduction of human growth hormone transgene in mice results in mammoth mouse phenotype, where as expression of the same transgene in pig results in premature death of transgenic pigs. (Pursel VG et al J. Reprod Fert. Sup 40: 235-245 1990, see page 235, para.1).

Furthermore, many biochemical pathways are plastic in nature, which reflects the ability of the embryo to use alternative gene when the preferred gene is modified. It is known in the art that the level and the specificity of a transgene as well as the phenotype of the transgenic animal are greatly dependent upon the specific expression vector used. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, for example are the important factors that govern the expression of a transgene. (Kappel et al. Current Opinion in Biotechnology 3:558-553 1992; see page 550, col.1, para. 3-4, page 548, col.2 para.2).

Furthermore, the phenotype of targeted mutations by a homologous recombination have not always been as predicted because the homologous recombination is a rare event which

requires numerous step that often fails. The embryonic stem (ES) cells are very sensitive to culture conditions and have natural tendency to differentiate, giving rise to unstable genome. The homologous recombination is a rare event in ES cells and the injection of ES in the blastocyte is highly unpredictable (Viville, in Transgenic Animals, Houdebine (eds), Harwood academic publishers, France. pp307-321, 1997).

At best the specification teaches insertion of I-Sce-I site via homologous recombination in mouse NIH3T3 fibroblast and mouse PCC7-s multipotent cell lines using viral vectors (page 64, para.3, page 67, table-1). The specification only exemplified the retroviral infection of a mouse PCC7-s multipotent cell line using viral vectors and fails to disclose that implantation of any selected clone lead to the making of a trasgenic mouse (page 64, para.3, page 67, table-1). Furthermore, the specification teaches genetic recombination, especially the homologous recombination in the making of transgenic yeast (page 3, para.1-2, example 1, 2 and 3). Based upon these results the specification merely speculated that "the method can also be used with transgenic animals" (page 85 para.1, para.3). The scope of instant claims encompass a transgenic mouse encoding any and all Group-I intron encoded endonucleases (The Group-I intron encoded endonucleases encompass any and all endonucleases encompassed by Class I, II, III, IV, and V I-endonucleases, wherein the Class I I-endonucleases encompass I-SceI, I-SceIV, I-CsmI and PanI endonucleases). The scope of instant claims also encompass a method for activation of any and all genes in a mouse cell by cleaving any Group I intron encoded endonuclease recognition site wherein the cleavage promotes the activation of expression of the gene by homologous recombination. The specification even fails to disclose any transgenic mouse comprising a nucleotide sequence encoding I-SceI wherein the I-SceI is introduced by homologous or non-homologous recombination. Furthermore, the methods of generating, culturing the transgenic cells, are not enabled because the method (as claimed) requires the use of cells obtained from a transgenic mouse.

Furthermore, considering the unpredictability in the transgenic art (*supra*) and the guidance provided in the specification it is unclear how one skill in the art would use D3 embryonic stem cells without excessive and undue amount of experimentation to generate

variety of transgenic mice encoding any and all Group-I intron encoded endonuclease sites. Viville's clearly states that although D3 embryonic stem cell line is an excellent embryonic stem cell line, creating a transgenic mice is not as easy task because technique is very long and there are many steps that often fails. To make and test is not the standard for enablement. The phenotype of a tansgenic animal is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. The applicant fails to disclose a single working example that encompasses the invention as claimed. It is unclear how one skill in the art would exercise the invention as claimed when the phenotype of a transgenic mouse (as required) is not known. Furthermore, considering the unpredictability in the transgenic art transgenic yeast or transfection of mouse cell lines in vitro does not recapitulate the complexities involved in the making of transgenic animals.

Thus, in view of lack of specific guidance in the specification, the skilled artesian at the time of filing would be unable to use the invention as claimed, without an excessive and undue amount of experimentation. Although, one skilled in the art would have been able to make the required genetic constructs encoding any and all Group-I intron encoded endonuclease sites, it would have required excessive and undue experimentation to make transgenic mice encoding any and all Group-I intron encoded endonuclease sites, without a predictable degree of success because the specification only provide guidance to make a transgenic yeast or transfected mouse cells encoding I-SceI site.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah

Clark can be reached on (703) 305-4051. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Tracey Johnson, whose telephone number is (703) 308-0377. If the claims are amended canceled and/or added the applicants are advised to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov).*

S. Kaushal, AU 1633

SUMESH KAUSHAL
PATENT EXAMINER